Normal tissue injury responses in mammary glands after low doses of ionizing radiation.

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Our goal is to better understand the signaling pathways and mechanisms that control radiation induced normal tissue injury and breast cancer risk and how they depend on dose and genetic background. Breast cancer is the second leading cause of cancer death in U.S. women. Treatment usually includes exposing the tumor to high levels of ionizing radiation. However, this always involves the irradiation of adjacent normal tissue leading to variable amounts of normal tissue injury, which potentially increases the risk of normal tissue complications including a second primary tumor. The degree of normal tissue injury after radiation varies with exposure regimen, tissue sparing protocol, and responses can vary among people but the underlying mechanisms are not well understood. To begin to address this variation in tissue injury after radiation we take advantage of the variation in sensitivity to radiation induced mammary gland cancer in three genetically defined inbred strains of mice (BALB/c: sensitive; C57BL/6 and SPRET/EiJ: resistant).

We are investigating the *in vivo* low dose tissue response in the mammary gland of BALB/c and C57BL/6 mice by studying gene expression responses after repeat fractionated low-dose exposures (Marchetti et al; poster presentation). Female mice were exposed to four weekly doses of 7.5 cGy. Four weeks after the last exposure we harvested the mammary gland proper for global gene expression analysis. In the mammary gland of BALB/c mice we found evidence of tissue injury and inflammation involving upregulation of ITGAX, RELB, SERPINA1, MMP12, FGF13, RSPO1 and FGG as well as upregulation of many genes involved in mitosis. Neither observation was present in the mammary gland of C57BL/6 mice suggesting that (1) the radiation response after low dose exposure is strain specific and (2) the tissue injury response is more pronounced in BALB/c mice 1 month after radiation exposure.

We hypothesize that the difference in radiation-induced tissue injury and mammary cancer risks between these mice may in part be due to a differential stromal response. The principal component of the extracellular matrix are fibroblasts, whose main functions include deposition of ECM, regulation of epithelial differentiation and tissue repair after damage. Dysfunction of stromal fibroblasts after exposure to IR can lead to impaired wound healing, fibrosis and altered behavior of nearby normal or tumor epithelial cells. To address our hypothesis we have started isolating mammary fibroblasts of BALB/c and SPRET/EiJ mice. A progress report of our work will be presented at the workshop.

[Supported by the U.S. Department of Energy; DE-AC02-05CH11231 (LBNL) with funding from the DOE Low Dose Radiation Research Program and LDRD (AMS)]